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EXAMINER

1802/1004

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ART UNIT	PAPER NUMBER
1806	7

DATE MAILED: 10/04/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. Aproge
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-16 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-16. are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Claims 1-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite in use of the parenthetical expression (type I), in that it is unclear whether the applicant intends that this language be present in the claim or not. Claim 10 is indefinite in that members of a Markush group should be mutually exclusive of each other, and the language "combinations of the foregoing" renders the claims indefinite. Furthermore, the claims should be written in proper Markush format, eg.".... selected from the group consisting of ....". Similarly, claim 11 should be written in proper Markush format.

Wdraw

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to show how to make and/or use the invention, eg. failing to provide an enabling disclosure. Claim 8 is drawn to a method of preventing insulin dependent diabetes by administering to an individual, prior to the development of diabetes, an anti-VLA4 antibody. There is no guidance in the specification for determining when the appropriate time "prior" to development of diabetes, the antibodies are to be administered. The examples presented in the specification, include data wherein adoptive transfer of spleen cells into NOD mice did not result in diabetes, due to treatment of the

spleen cells with anti-VLA4 (more specifically antibodies which bind to the B epitope of VLA4). There is no guidance in the disclosure to extrapolate the situation presented with the NOD mice to humans. When during the transfer of the spleen cells corresponds to "prior" to onset in humans. There are no parameters for determining the adequate time "prior" to the development of overt diabetes. The language "prior" includes a day before, or even ten years before the development of the disease. There is also no guidance for determining the duration of the treatment. Does the treatment last one day, 10 days or 10 year? How does the two week post transfer treatment in NOD mice translate to treatment in humans? Due to the lack of guidance presented in the specification, one of ordinary skill in the art would be forced into undue experimentation in order to carry out the invention as claimed.

Claims 10-16 are drawn to a method of treating diabetes by administering "fragments of antibodies" to VLA4, or polypeptides which bind to VLA4 in an amount "effective" to provide inhibition of onset of diabetes and a pharmaceutical composition of the antibody for treating diabetes.

First, there is no indication in the specification that binding peptides specific for VLA4 have any effect on any form of diabetes, other than Type 1 diabetes. The mechanism of onset for other types of diabetes has not been shown to be identical to the mechanism of onset for type 1 diabetes.

Second, there is no guidance in the specification for the various antibody fragments or binding peptides or molecules which can treat diabetes. The language antibody fragments and peptides or small molecule, encompasses a variety of substances, anywhere from a single amino acid to an inorganic molecule. One of ordinary skill in the art would be forced into undue experimentation in order to first, make or isolate the myriad substances encompassed in the claims, and second to determine the amount sufficient to provide inhibition of onset of diabetes. There are no parameters for determining the amount effective to prevent onset of diabetes, using an inorganic molecule for example.

Claim 15 is drawn to a method of treatment of diabetes by administering an amount of antibody sufficient to provide plasma levels of "at least" 1 micrograms per milliliters. The language "at least" has no upper limit and includes concentration in beyond gram quantities. There is no enablement in the specification for the treatment of diabetes using milligram or gram quantities of anti-VLA4 antibodies for treatment of diabetes. It is suggested that a range of concentrations which is enabled in the specification be recited in the claims.

Claims 1-16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

35 U.S.C. § 101 reads as follows:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.**

The specification is objected to under 35 U.S.C. § 112, first paragraph, and claims 1-16 are rejected under 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 101, as the specification fails to adequately teach how to effectively use the claimed method for prevention or for the treatment of type I diabetes and the claimed inventions appear to lack patentable utility. The specification provides no exemplification of how to use the claimed method for successful treatment of type 1 diabetes and provides insufficient evidence that the claimed methods have therapeutic utility. The asserted utility of the claimed method appears to be based solely on data obtained from the transferred model of NOD mouse. The spleen cells which were transferred to the NOD mice were treated with the R1-2 mAb which is an antibody specific for the B epitope of VLA4. The antibody was than administered to the transfer model for two weeks in order to coat the VLA4 positive cells. In general, data such as that disclosed in the specification, cannot be extrapolated to predict human efficacy <u>in</u> <u>vivo</u> as it would be impossible to duplicate the saturation of spleen cells with the desired antibodies prior to onset of the disease. It would appear that although the NOD model is effective in studying the onset of diabetes, it is not

sufficiently correlative of therapeutic utility. It should also be noted that the use of antibodies for human therapy has not fulfilled its original promise as is indicated by Waldmann and Harris et. al. (attached).

Waldmann, in a recent review of the literature pertaining to clinical applications of monoclonal antibodies for diagnosis and therapy of human disease, teaches that effective therapy using monoclonal antibodies has been extremely limited. Waldmann also teaches that in general, in vitro and animal model data have correlated poorly with results obtained with human subjects in clinical trials. Harris has echoed this sentiment and has gone one step further in stating "there is widespread acceptance that there is little future for the use of rodent mAbs in human therapy." Harris does however, say that humanized antibodies show some potential, but is unwilling to definitively commit to this view until further "clinical" data has been presented and evaluated. In view of the contemporary knowledge in the art of the general lack of successful application of monoclonal antibody-based therapy methods for the treatment of human diseases and of the limited predictive value of in vitro results for efficacy in humans, it does not appear that those of skill in the art would view applicant's assertions that the claimed antibody-based therapy methods are useful for treatment of diabetes based only on the limited data in the specification on pages 23-27 and in the absence of further experimental evidence

establishing the utility of the claimed methods.

The provisions of 35 USC § 101 require that the claimed subject matter must be useful in order to be eligible for patentability. Case law has established that utility must be definite and in currently available form, not based on mere assertion. Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). Where the asserted utility would not be believable on its face to persons skilled in the art in view of the contemporary knowledge in the art at the time the application was filed, as is the case here, the burden is upon the applicant to provide proof of the utility of the claimed inventions. Applicant must provide proof of the utility of the claimed methods which would be convincing to those of skill in the art that the utility of the claimed medicaments is sufficiently established. See In re Irons, 340 F.2d 924, 144 USPQ 351 (CCPA 1965); Ex parte Krepelka, 231 USPQ 746 (PTO Bd. Pat App. & Inter. 1986); and Ex parte Chwang, 231 USPQ 751 (PTO Bd. Pat. App. & Inter. 1986). Note that when utility is directed to humans, the data must generally be clinical, however, adequate animal data would be acceptable in those instances where one of ordinary skill in the art would accept the correlation to human utility. In order to accept animal data, there must exist an art recognized model for testing purposes.

It should also be noted that the exemplification of the successful use of a single antibody for the treatment of a single disorder would not be enabling for the invention as broadly claimed.

As discussed by Waldmann, the efficacy of antibody-based treatment methods is significantly affected by many different antibody variables and there is no clear teaching of the characteristics of the R1-2 antibody which confer the positive effects noted in the experiments.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless--

(b) the invention was patented or described in a printed publication in this country or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 16 is rejected under 35 U.S.C. § 102(b) as being anticipated by Issekutz et. al..

The claim is drawn to a pharmaceutical composition comprising an antibody which recognizes VLA4, wherein the composition is in a pharmaceutically acceptable carrier and is able to prevent onset of diabetes. First, it should be noted that the intended use clause in the claim has no patentable weight on the examination of the product, which is an anti-VLA4 antibody. Second, it should be stated that the general buffer which contains the monoclonal antibody, eg. water or PBS, is a pharmaceutically acceptable carrier.

The reference teaches the use of TA-2, an IgG-kappa antibody specific for VLA4, for inhibiting lymphocyte migration <u>in vivo</u> (see

Materials and Methods and Figure 1).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lila Feisee whose telephone number is (703) 308-2731.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO FAX Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 FAX Center number is (703) 308-4227. The hours of operation of the Center are 8:45 am - 4:45 pm, Monday - Friday.

Feisee/lf
October 1, 1993

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
10/1/93